

REMARKS

Claims 1-21 are canceled. Claims 22-29 are pending.

Claims 22-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deihl (WO 94/13280) in view of Fassberg et al (EP 0656206) and further in view of Kanios et al (U.S. Patent No. 5,719,197).

Independent claim 23 recites a method of administering a pharmacologically active compound to a mammal comprising spraying the oral mucosa of the mammal with a propellant free buccal spray composition containing a pharmacologically active compound and a polar solvent. According to independent claim 23, the active compound comprises a central nervous system active amine, a sulfonyl urea, an antibiotic, an antiviral, a sleep inducer, an antiasthmatic, an antiemetic, a histamine H-2 receptor antagonist, a barbiturate, a prostaglandin or a bronchial dilator.

The Office Action asserts that Deihl provides “general teachings of formulations for buccal mucosal administration” (Office Action at 4). The Office Action acknowledges, as it must, that Deihl fails to disclose any of the active compounds recited by any of the claims, and also fails to disclose the use of the presently claimed solvents or amounts, including polyethylene glycol or non-polar solvents.

Based on the alleged “general teaching” of Deihl, the Office Action asserts that it would have been obvious to “have looked in the art for other specific solvents suitable for spray formulations of liquid carriers, as taught by Fassberg et al., with reasonable expectations of successfully preparing suitable formulations for various therapies.” (Office Action at 4). The Office Action also asserts that “ it is obvious to one of ordinary skill in the art to have substituted any suitable active agent for the analgesics of Deihl’s buccal spray formulations as...taught by Kanios et al.” (Office Action at 5, emphasis added).

Thus, the Office Action is premised on the PTO’s reading of Deihl as a general teaching from which one may allegedly extrapolate to multiple other solvents and amounts, and to other

pharmaceutically active agents, and do so with a reasonable expectation of success. Remarkably, this reasoning is based on Fassberg et al., which is not directed to propellant-free sprays as claimed, and on Kanios, which is not directed to buccal sprays at all. Aside from the shortcomings of these secondary references, Deihl itself is far from a general teaching of buccal sprays from which one of ordinary skill at the time of the present invention would have expected much of anything at all, much less that one of ordinary skill would have been motivated to modify Deihl to achieve the presently claimed methods for administering the recited active compounds.

More specifically, at the time of the present invention, Deihl would not have been considered a credible or relevant teaching and, for the reasons discussed below, would not have been relied upon in any capacity by those skilled in the art at the time that the present invention was made. Deihl purports to teach a sprayable analgesic composition where an analgesic is capable of being absorbed into the bloodstream through the buccal mucosa. Deihl's composition includes ibuprofen or acetaminophen and aqueous ethanol. Deihl states that for treatment of a headache, a patient sprays four measured sprays into the mouth. Each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This treatment is repeated once after five minutes. That is, Deihl teaches a total dose of 4-8 milligrams of acetaminophen or ibuprofen. Deihl at 5.

Even assuming 100 percent bioavailability, those of ordinary skill in the art would readily appreciate that a 4-8 milligram dose of acetaminophen or ibuprofen is not even remotely therapeutically effective. According to GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed., the oral dosage for acetaminophen is 320 to 1000 milligrams for adults and 40 to 480 milligrams for children with about 88% bioavailability. For ibuprofen the oral dosage for adults is 400 milligrams for mild pain to as much as 3200 milligrams for arthritis, with about 80% bioavailability. Thus, even assuming 100% bioavailability, a patient receiving Deihl's formulation would receive only 4-8 milligrams of active agent, a tiny fraction of what is required for any therapeutic effect. A patient would need to administer a completely unworkable number of spray activations of Deihl's formulation to realize any potential therapeutic effect, but by that point the volume and fluid sprayed would be so great as to result in swallowing and thus avoid mucosal

absorption. Therefore, one of ordinary skill in the art would have readily appreciated that Deihl's spray composition and method is unworkable and ineffective.

One of ordinary skill in the art would also have appreciated that Deihl's ineffective, unworkable spray teachings were quite consistent with the state of the art at the time the present invention was made. Those skilled in the art generally perceived buccal administration as an ineffective and unworkable delivery method. For example, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710, states that "when only small amounts of drugs are required to gain access to the blood, the buccal route may be satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route." (Emphasis added).

This well accepted view of buccal administration is based in part on the belief that the relatively rapid clearing of the mouth by swallowing limited the buccal absorption phase to between about 5-10 minutes. Therefore, it was understood that the amount of drug delivered would be very small causing the blood plasma levels of drugs administered buccally to rise slowly. Thus, buccal administration was generally disfavored and thought to be an ineffective and unworkable delivery method. Consequently, the disclosure of Deihl itself, as well as the general understanding in the art, were completely inconsistent with the Office Action's assertions and reasoning that Deihl provides a general teaching from which one of ordinary skill would have been motivated to extrapolate to diverse pharmaceutical actives and solvents, much less to do so with any expectation of success in administering a pharmaceutically effective amount of such actives via a buccal spray.

In addition, Fassberg et al. relates to an inhalation aerosol, which is a propellant-containing spray or powder formulation for oral and/or nasal administration. Fassberg et al. does not disclose or suggest any propellant-free method for the delivery of an active agent by spraying the buccal mucosa of a mammal. Fassberg et al. clearly does not teach or suggest that buccal administration of any actives is generally effective.

According to the PTO, it would have been obvious to modify Diehl with the solvents disclosed by Fassberg et al. (Office Action at 5.) To the contrary, one of ordinary skill would not have used the Fassberg et al. solvents to modify the formulations of Diehl, because Fassberg et al. explains that the solvents used in its inhalation formulations are only present to facilitate the propellant. Diehl has no propellant and the present claims exclude propellants. Accordingly, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Fassberg et al., for this additional reason.

Likewise, one of ordinary skill in the art would not have been motivated to modify Diehl with the teachings of Kanios et al. to achieve the compositions and methods recited by the presently pending claims. Kanios et al. refers to an intermediate composition that is made into a “finished dosage form” by applying a flexible backing which further defines the size and shape of the finished dosage form, which is, among other things, occlusive to water permeation in vivo. Kanios et al. is entirely unrelated to a buccal spray method for transmucosal administration.

Consequently, none of the prior art of record alone or in any combination teaches all elements of the present applicants’ independent claims. In particular, none of the art teaches transmucosal absorption of a pharmacologically effective amount of the claimed active compounds by spraying the oral mucosa. Moreover, the state of the art, including Remington: *The Science and Practice of Pharmacology*, teaches away from the Applicants’ invention as presently claimed. Remington demonstrates that “only a few drugs may be given successfully by [the buccal spray] rate” and Deihl’s method was apparently unsuccessful. Furthermore, in addition to the general but significant bias in the art (at the time of the invention) against buccal spray administration, Applicants have discovered surprisingly beneficial results from their use of a buccal spray which further supports the non-obviousness of the claimed invention. See, e.g., specification at paragraph [0003] and [0025]. For at least these reasons, Applicant respectfully requests that this § 103 rejection be withdrawn.

Claims 22-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu (WO 9303751) in view of the Physician's Drug Reference (PDR). This rejection is respectfully traversed.

The Office Action uses Fu as a general teaching from which one of ordinary skill could have allegedly extrapolated to any other pharmaceutical active, and have done so with an expectation of success, based on "the general teachings of formulations for buccal mucosal administration of Fu" (Office action at 5-6). The Office Action is mistaken, as Fu is anything but a general teaching that would have motivated one of ordinary skill to look to the PDR with any expectation of success, and the general state of the art at the time of the present invention was to the contrary.

As discussed above, those skilled in the art generally perceived buccal administration as an ineffective and unworkable delivery method. See, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710. Fu refers to compositions for the sublingual delivery of specific polypeptides that are normally degraded upon oral administration. Fu is directed to the administration of polypeptides that can not be ingested. These polypeptides are very limited in scope. Fu only present examples of formulations containing leuprolide acetate and deslorelin acetate, which is closely related to leuprolide acetate. At most, Fu establishes that buccal administration can be used for specific polypeptides and only when a permeation enhancer is employed. See e.g., Fu at 10-12 (showing low bioavailability for exemplary formulations, less than 25% bioavailability for all but one formulation). This underscores the general state of the art regarding the problem with buccal delivery as described by Remington.

The examples provided by Fu are limited to two closely related polypeptides that can not be administered by oral ingestion. Thus, Fu would not have been viewed as a general teaching for successful buccal administration of a variety of pharmaceutical actives. Therefore, one of ordinary skill in the art would not have been motivated to modify Fu with the pharmaceutical actives of the PDR, or expect that such a combination would have been viable for administering an effective amount the claimed actives, as stated in the Office Action.

Consequently, none of the prior art of record alone or in any combination teaches all elements of the present applicants' independent claims. In particular, none of the art teaches transmucosal absorption of a pharmacologically effective amount of the claimed actives by spraying the oral mucosa. Furthermore, in addition to the general but significant bias in the art (at the time of the invention) against buccal spray administration, that the Applicants have discovered surprisingly beneficial results from their use of a buccal spray further supports the non-obviousness of the claimed invention. See, e.g., specification at paragraph [0003] and [0025]. For at least these reasons, Applicant respectfully requests that this rejection be withdrawn.

Double Patenting

Claims 22-29 are rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims of U.S. patents 6,110,486; 5,955,098; 5,869,082; 6,969,508; 6,977,070; and 6,998,110. Claims 8-29, 31, 65-86, 91 and 124-134 are also provisionally rejected over claims of several co-pending applications. As the claims of the present application, as well as those of the co-pending applications are subject to change, Applicant respectfully requests that these rejections be held in abeyance until such time as this application is otherwise in a condition for allowance.

Except for the double patenting issues, each of the presently pending claims in this application is believed to be in a condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims. Should the Examiner believe that anything further may be requested to place this application in even better form for allowance, the Examiner is cordially invited to telephone the undersigned attorneys for Applicants.

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